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Highly Enantioselective Copper-Phosphoramidite-Catalyzed Conjugate Addition of Dialkylzinc Reagents to Acyclic α,β-Unsaturated Imides

Mauro Pineschi,* Federica Del Moro, Valeria Di Bussolo, Franco Macchia

Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy
Fax: (+39)-(0)50-221-9660, e-mail: pineschi@farm.unipi.it

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Abstract: A new and practical way to introduce an alkyl fragment in the β-position of aliphatic carboxylic acid derivatives with high enantioselectivities by the use of a commercially available chiral ligand is reported. *N*-Acylpyrrolidinones, as simple derivatives of an α,β-unsaturated carboxylic acid, were found to be the substrates of choice featuring good reactivity and high enantioselectivities (up to > 99% ee).

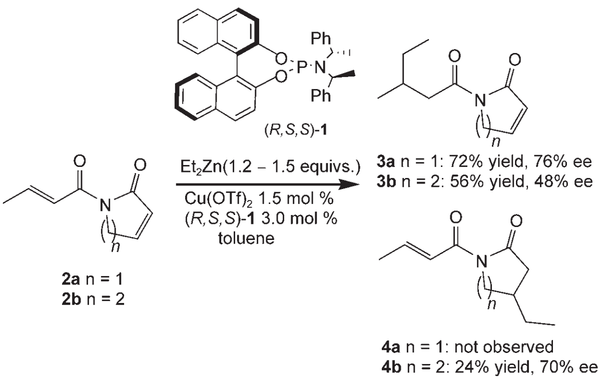
Keywords: asymmetric catalysis; C–C bond formation; conjugate addition; copper; phosphoramidite ligands; zinc

The asymmetric conjugate addition (ACA) of organometallic reagents to α,β-unsaturated carbonyl compounds has been the subject of intensive research activity in the past few years.[1] However, highly enantioselective catalytic procedures which make use of acyclic unsaturated carboxylic acid derivatives are rare.[2] The high conformational mobility of these species, together with the presence of only feeble substrate-catalyst steric and electronic interactions, makes the design of effective highly enantioselective systems a real challenge. Whereas chiral imides have been widely used to perform efficient ACA in the context of a chiral auxiliary approach,[3] the addition of alkylmetals to the enantiotopic faces of α,β-unsaturated imides remained problematic until Hoveyda's recent report on the asymmetric addition of dialkylzinc reagents to *N*-acyloxazolidinones promoted by modular triamide phosphanes.[4] However, high enantioselectivities were reached only with β-alkyl derivatives whereas, for example, simple β-aryl derivatives proved to be only poorly reactive and β-vinyl derivatives were not considered. Moreover, it has been suggested that conventional chiral ligands developed for enones were not suitable for the 1,4-addition of R_2Zn to aliphatic bidentate substrates with chiral metal catalysts, pointing to an apparent need for specialist ligands.[5]

We report here the development of a simple, practical and highly enantioselective copper-catalyzed 1,4-addition of alkylmetals to acyclic α,β-unsaturated carboxylic acid derivatives, based on the use of modular (bidentated) cyclic imides and the commercially available phosphoramidite chiral ligand **1**, developed by Feringa et al.[6]

We recently reported a new copper-catalyzed ACA of organometallic reagents to α,β-unsaturated lactams bearing appropriate protecting-activating groups on the nitrogen atom.[7] The use of carbonyl protecting groups on the endocyclic nitrogen of γ- and δ-lactams was essential to attain their reactivity and to reach high ees of the corresponding conjugate adducts. In the search for a new carbonylic protecting-activating group for the nitrogen, we considered the 2-butenoyl moiety. The copper-phosphoramidite (*R*,*S*,*S*)-**1** catalyzed addition of Et_2Zn to compounds **2a** and **b**, each containing two conjugated double bonds of a different nature, afforded a reaction mixture in which the addition occurred predominantly on the acyclic framework, to give adducts **3** with a moderate to good enantioselectivity (Scheme 1).

The use of imides **5a** and **b**, which are devoid of the endocyclic double bond, gave improved yields and enantioselectivities with respect to compounds **2a** and **b** (entries 1 and 2, Table 1). It is interesting that the small steric and electronic differences present in compounds **2a**, **b** and **5a–d** have such an important effect on the enantioselectivity. Imide **5c**, containing a 2-azepanone, gave the lowest ee (38%, entry 3) whereas the oxazolidinone moiety, successfully used by Hoveyda,[4] gave only a 64% ee in our reaction conditions (entry 4), while the highest ee (87%) was obtained with 2-pyrrolidinone as the *achiral template*. The fact that α,β-unsaturated amides **5e** and **f** were not reactive in our reaction conditions (Table 1, entries 5 and 6), further confirmed our ex-



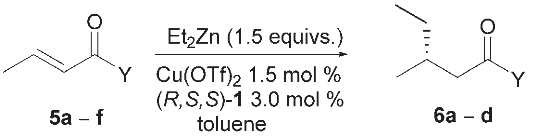
Scheme 1. Catalytic enantioselective addition of Et$_2$Zn to 2-butenoyl α,β-unsaturated lactams **2a** and **b**.

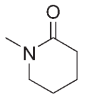
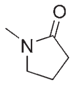
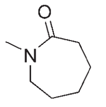
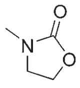
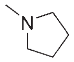
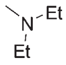
pectations that the presence of a carbonyl group on the nitrogen, i.e., a bidentate substrate, was mandatory in order to obtain the corresponding adducts with appreciable yields and enantioselectivities.

Having identified the *optimal achiral template*, next we examined the scope of our system in reactions with several β-substituted α,β-unsaturated *N*-acyl-2-pyrrolidinones.[8] The results, summarized in Table 2, indicate that different groups in the β-position participate successfully in the enantioselective conjugate addition.

Our reaction protocol worked particularly well with cinnamyl substrates, giving an efficient catalytic formation of benzylic carbon stereocenters (entries 4–13). In *p*-substituted cinnamyl substrates **7d–g** there is a major electronic effect, with a clear relationship between the electronic effects and the enantiomeric excesses of the corresponding adducts, the stronger electron-withdrawing substituents (*p*-CF_3, *p*-Br) showing the higher enantiomeric excesses (Table 2, entries 7 and 8). To the best of our knowledge, there appears to have been no system-

Table 1. Individuation of the optimal achiral template by copper-phosphoramidite catalyzed addition of Et$_2$Zn to crotonic acid derivatives.[a]



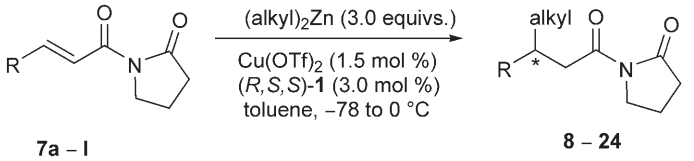
Entry	Substrate (Y=)	Conditions	Conversion [%][b] Product	ee [%][c]
1	 **5a**	6 h, –78 to 0 °C	98 (56) **6a**	56
2	 **5b**	2.5 h, –78 to –20 °C	>98 (75) **6b**	**87** (*R*)
3	 **5c**	6 h, –78 to 0 °C	98 (65) **6c**	38
4	 **5d**	4 h, –78 to 0 °C	98 (60) **6d**	64
5	 **5e**	6 h, 0 °C	No reaction	–
6	 **5f**	6 h, 0 °C	No reaction	–

[a] All reactions were carried out in accordance with the general procedure by the use of 1.5 equivs. of Et$_2$Zn.

[b] Conversions were determined by ^{1}H NMR of the crude product. Yields of isolated product after chromatography on SiO_2 are reported in parentheses.

[c] Determined by HPCL on a Daicel Chiralpak AD-H or Daicel Chiralcel OD-H. Absolute configuration determined by correlation with known compounds.

Table 2. Copper-catalyzed addition of dialkylzincs to α,β-unsaturated *N*-acyl-2-pyrrolidinones.[a]



Entry	R (7)	Alkyl	T [h]	Conversion [%][b]	Product	ee [%][c]
1	(**a**) Pr	Et	3	>98 (80)	**8**	84
2	(**5b**) Me	*i*-Pr	3	>98 (78)	**9**	60
3	(**b**) *i*-Pr	Et	2	>98 (75)	**10**	95
4	(**c**) Ph	Et	3	>98 (78)	**11**	98 (*S*)
5	(**c**) Ph	Bu	6	95 (62)	**12**	85
6	(**c**) Ph	*i*-Pr	4	>98 (75)	**13**	81
7	(**d**) p-BrC$_6$H$_4$	Et	3	>98 (82)	**14**	>99
8	(**e**) p-CF$_3$C$_6$H$_4$	Et	2	>98 (84)	**15**	>99
9	(**f**) p-OMeC$_6$H$_4$	Et	4	>98 (74)	**16**	94
10	(**g**) p-CH$_3$C$_6$H$_4$	Et	4	>98 (88)	**17**	94
11	(**h**) m-CF$_3$C$_6$H$_4$	Et	4	92 (55)	**18**	94
12	(**i**) o-BrC$_6$H$_4$	Et	4	>98 (78)	**19**	80
13	(**j**) o-CH$_3$C$_6$H$_4$	Et	4	90 (44)	**20**	87
14	(**k**) (*E*)-CH$_3$CH=CH	Et	16	75 (16)	**21**	96
15	(**l**) 1-cyclohexenyl	Et	16	38 (7)	**22**	n.d.
16	(**a**) Pr	Me[d]	4	>98 (70)	**23**	36
17	(**f**) p-OMeC$_6$H$_4$	Me[d]	4	>98 (65)	**24**	20

[a] All reactions were carried out in accordance with the general procedure.
[b], [c] See corresponding notes of Table 1.
[d] Reactions carried out with AlMe$_3$ (1.5 equivs.)

atic study of how purely substrate electronic effects influence the degree of asymmetric induction for a catalytic ACA reaction. However, even if there was a qualitative correlation between the substrate's electronic properties and the enantioselectivity of the corresponding adducts, an exact correlation of Hammett sigma-*p* constants and enantioselectivity proved not to be linear.[9]

While the addition of bulky Grignard reagents to α,β-unsaturated esters exhibited a poor efficiency in terms of conversion and enantioselectivity,[2] our enantioselective CA was not limited to linear organozinc reagents, and also (i-Pr)$_2$Zn gave satisfactory results (Table 2, entries 2 and 6). The addition of dialkylzincs to β-alkenyl α,β-unsaturated pyrrolidinones was also addressed. The reaction of pyrrolidinone **7k**, derived from sorbic acid, proved to be slower and the conversion was not complete even after a long reaction time, and an even lower reactivity was displayed by β-cyclohexenyl-susbtituted substrate **7l** (Table 2, entries 14 and 15). However, one of the corresponding 1,4-adducts, **21**, was obtained with a high ee, albeit with low yield (entry 14). It is worth mentioning that it was not possible to isolate any adducts deriving from a 1,6-addition pathway, even if their presence in minor amounts in the relatively complex crude mixture cannot be ruled out.[10]

A limitation of our reaction protocol is the scarce reactivity of Me$_2$Zn, which can be by-passed through the use of the more reactive organoaluminum reagents.[7] Also with α,β-unsaturated *N*-acylpyrrolidinones **5b** and **7a**, **f**, it was possible to transfer an Me group only by the use of AlMe$_3$, although the corresponding reactions proceeded only with modest ees (Table 2, entries 16 and 17). Interestingly, in a separate set of experiments, we found that by the use of organoaluminum reagents rather than organozinc reagents (AlEt$_3$ instead of Et$_2$Zn), enantiomeric products were obtained using the same chiral catalyst (data not shown in Table 2). This is an indication that the structure of the active catalyst incorporates a substrate binding pocket which depends on the nature of the organometallic reagent.

Optically enriched β-alkyl-*N*-acyl-2-pyrrolidinones may easily be converted into the corresponding β-substituted esters by simple treatment with a catalytic amount of Er(OTf)$_3$ in EtOH,[11] or hydrolyzed [12] to the corresponding carboxylic acid (see Supporting Information).[13]

Probably, the delocalization of the nitrogen lone pair in the endocyclic carbonyl reduces the donation to the carbonyl adjacent to the α,β-unsaturation, and thus contributes to an increase in the reactivity of the β-position. Moreover, it is reasonable to hypothesize a chelation by the zinc ion of the two carbonyl oxygens, and the formation of a highly organized cluster, which is in turn responsible for the high enantioselectivity. The chelation is able to enhance the electrophilicity of the β-carbon, and ensures a good enantiofacial control by blocking the substrate in a dominant reactive conformer, which is most probably the *s-cis* one.[14]

To sum up, we have found a new and practical way to introduce an alkyl fragment in the β-position of aliphatic carboxylic acid derivatives with high enantioselectivities by the use of a commercially available chiral ligand.

Experimental Section

General Procedure for the Copper-Phosphoramidite ACA

A flame-dried Schlenk flask was charged with $Cu(OTf)_2$ (2.5 mg, 0.0069 mmol) and (*R*,*S*,*S*)-1 (7.5 mg, 0.00128 mmol) in anhydrous toluene (1.0 ml) and the mixture was stirred at room temperature for 40 min. The colorless solution was cooled to −78 °C and subsequently, a solution of the *N*-acylpyrrolidinone (0.46 mmol, dissolved in the minimal amount of toluene or CH_2Cl_2) and the organometallic reagent (0.69–1.38 mmol), were added under an Ar atmosphere. The reaction was monitored by TLC analysis, quenched with saturated aqueous NH_4Cl and extracted several times with Et_2O. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product that was purified by flash chromatography.

See Supporting Information for characterization data of all new compounds, ee determinations, conversion to carboxylic acid derivatives, determination of absolute configurations, and Hammett plots.

Acknowledgements

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